UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/868,879	06/22/2001	Julian Schofield	55908(46322)	9973

7590 07/02/2004

Edwards & Angell, LLP
Intellectual Property Practice Group
P.O. Box 55874
Boston, MA 02205

EXAMINER	
MARVICH, MARIA	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/868,879	SCHOFIELD ET AL.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *1-3,5,6,12, 15 and 21-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,7-10,13,14 and 17-20* is/are rejected.

7)☒ Claim(s) *11 and 16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 June 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/18/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

This office action is in response to a response to a restriction requirement filed 4/26/04. Claims 1-45 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group IV in the reply filed on 4/26/04 is acknowledged. The traversal is on the ground(s) that restriction practice under 35 USC 121 is not applicable to applications filed under Rule 371 (see MPEP 1895.01(D). It is suggested that Unity of Invention is controlling where applicants elected Invention I (Claims 1-4, 7-27, 40 and 42). However, applicants have elected Group IV and furthermore requested rejoinder of Groups IV and V. Rejoinder of Groups IV and V are said be without due burden as the IPER has provided a review of the literature which indicates that claims 1-4, 7-27, 40 and 42 are novel. Also, Group IV and V are related in that a review of the literature for Group IV would overlap substantially with the search conducted by the International Authority and a search for Group V.

This is not found persuasive because the restriction mailed 3/22/04 was executed under unity of invention principles as set forth in 37 CFR 1.475 and 1.499. Under PCT Rule 13.2 the special technical feature lacks unity it does not represent a contribution over the prior art (Rhode et al). Applicants' statement that the lack of Unity set forth in the International Preliminary Examination Report is unsupported and is in fact inaccurate as restriction can occur at any time during prosecution before final action (see MPEP 1.142). Applicants' argument that Groups IV and V are without search burden is moot as under PCT practice for Lack of Unity search burden is not the standard.

The requirement is still deemed proper and is therefore made FINAL. Claims 1-3, 5-6, 12, 15 and 21-45 are withdrawn from consideration as being drawn to nonelected inventions. Claims 4, 7-11, 13-14 and 16-20 are examined herein.

Information Disclosure Statement

An IDS filed 6/18/02 has been identified and the documents considered. The signed and initialed PTO Form 1449 has been mailed with this action.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). Specifically, the citizenship of T. Rademacher has been altered.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Specifically, figures 1-8 contain sequences that are not identified by sequence identifier numbers. If the sequences can be found in

the sequence listing it would be remedial to insert the appropriate SEQ ID NO:s. If not, a new sequence listing, CRF and letter stating that the contents of the sequence listing and the CRF are the same and contain no new matter is required.

Claim Objections

Claims 11 and 16 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 4, 7-10, 13-14 and 17-20 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 7-10, 13-14 and 17-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4, 7 and 17 are rejected as claims must begin with "The" or "A".

Claims 4, 7-10, 13-14 and 17-20 provides for the use of GPI-PLD, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 7-10, 13-14 and 17-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in

the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The invention recites a use of glcosylphosphatidyl inositol specific phospholipase D (GPI-PLD) for the preparation of a medicament. The invention utilizes disciplines of protein purification and clinical technology.

2) **Scope of the invention**. The medicament is then used to treat conditions broadly described as those that respond to GPI-PLD or which are characterized by reduced levels of GPI-PLD as compared to a normal patient. Specifically recited conditions are diabetes or diabetic conditions, liver dysfunction or disorders involving pancreatectomies and endotoxin-induced conditions such as septic shock. These steps of therapy exacerbate the complexity of the invention.

3) **Number of working examples and guidance**. The specification teaches that diabetic complications such as insulin resistance may be caused by deficiencies in GPI-PLD. GPI-PLD is produced by the pancreas and in culture was shown to be secreted in response to insulin secretagogues (page 44, line 33 through page 45, line 4). Applicants describe prior art observations that suggest that the levels of GPI-PLD are responsive to the obese/diabetic genotype as observed in rat streptozotcin-induced diabetes mellitus in which insulin resistance correlated with the impairment of IPG metabolism. As well, mRNA for a GPI-PLD like gene was over-expressed in obese mice (see page 45, line 14-24). Therefore, applicants concluded that GPI-PLD could be used as a treatment for

diabetes (page 5, lines 6-20). As to the use of GPI-PLD to treat conditions mediated by infectious organisms, it is disclosed that endotoxins are believed to act by inhibiting GPI-PLD. No particular theory as to the mechanism of is provided (see page 8, line 10-15). There is no disclosure as to the association of GPI-PLD and liver dysfunction or pancreatectomies except that patients with liver disease have lower levels of active enzyme which is correlated with reduced albumin levels (page 45, line 8-12).

The disclosure states that GPI-PLD includes amino acid sequence variants, alleles active portions or fragments (page 15, line 1 through page 18, line 16). A variant has been identified by the instant inventors which differs from the amino acid sequence of human GPI-PLD at a phosphorylation site from amino acids 689-692 (see page 16, line 16-21). Other variants are those that are without signal peptide (page 15, line 15-19). Activity of the GPI-PLD is said to reside in the N-terminal 39 kD portion (see page 17, line 35 through page 18, line 1-5). In the working examples, applicants teach the identification and characterization of three clones obtained from human liver libraries-clones a1, b2 and d3. Clone a1 is a full length that differs in three positions from pancreatic GPI-PLD. Clones b2 and d3 are isoforms of a1. An *in vitro* cell culture system was established from which it was surmised that GPI-PLD is obtained from serum for second messenger signaling.

The specification lacks guidance as to doses or means of administration of GPI-PLD to individuals with the recited conditions. The specifics are left to the responsibility of general practitioners and other medical doctors (see page 24 , line 1-20). Instead applicants provide a general review of means of administration and pharmaceutical compositions (page 23, line 1-35).

State of Art. GPI-PLD was isolated in the 1980s as a plasma protein. Its characterization continues to date (Rhode et al, page 128, paragraph 4-5). GPI-PLD is relatively new art with incongruous information regarding its *in vivo* functions. Rhodes in addition to several other documents published at the date of filing of the instant invention was interested in correlating GPI-PLD with disease state (see Maguire et al Raymond et al and Rhode et al). In general these references demonstrate that patients with liver disease have lower activity of GPI-PLD than patients with healthy livers. Rhodes et al investigates the possibility that GPI-PLD is contributed from a variety of organs (see page 141, paragraph 3). And more recently, Deeg et al (Am J Physiol Endocrinol Metab 281:E147-E154, 2001) states that the tissue source for circulating GPI-PLD is unknown and whether serum levels are regulated is also unknown (see abstract). However, they do determine that in diabetes GPI-PLD levels are altered and are consistent with liver as a contributor to circulating GPI-PLD.

The use of GPI-PLD in medical treatment is a high art with little known. At the time of filing, its use in medicaments was not common. As described below, Anderson et al (US 2002/0048576) contemplates use of GPI-PLD in treating digestive tract infections such as by mycobacterium (see paragraph 0005).

5) **Unpredictability of the art**. The art of protein therapy utilizing GPI-PLD as a therapeutic against conditions that respond to GPI-PLD or are characterized by reduced levels of GPI-PLD such as diabetes, liver dysfunction or endotoxin-induced conditions is highly unpredictable. In general, protein therapy is unpredictable. Torchilin and Lukyanov (DDT Vol 8(6):259-266) teach that there are many unresolved problems concerning the delivery of proteins and peptides such as rapid elimination from the

circulation through renal filtration, enzymatic degradation, uptake by the reticuloendothelial system and accumulation in non-targeted organs and tissues and inefficient cell entry (see Box 1, page 260). However, the lack of guidance in the instant specification exacerbates this unpredictable art.

The instant invention relies on *in vitro* culture data to formulate an *in vivo* application of GPI-PLD. It is not clear that reliance on experimental models accurately reflects the relative superiority or efficacy of the claimed therapeutic strategy and applicants present no disclosed or art recognized nexus between the xenograft and nude mice experimental models and the human disease state. "Although animal studies have suggested low toxicity and excellent efficacy, these investigation have been limited by the use of immuno-deficient mice" (Meng and Deiry, Gene Therapy of Cancer, 1999, p. 6, column 1). The success of any *in vitro* assays or *in vivo* animal models cannot be considered as evidence of success of treatment, *in vitro* results rarely correlate well with *in vivo* clinical trial results in patients and have not translated into successful human therapies. Furthermore, any successes in the published document by Bent cannot be extrapolated back to the instant invention because the instant specification lacks support for the teachings of the reference.

6) **Summary**. The invention recites use of GPI-PLD as a medicament for use in conditions that respond to GPI-PLD or are characterized by reduced levels of GPI-PLD as compared to normal patients. The unpredictability of using the claimed invention is accentuated due to the lack of methods or processes disclosed in the instant specification that exacerbate a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Conclusion

Claims 4, 7-10, 13-14 and 17-20 are rejected.

Claims 11 and 16 are objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

June 25, 2004

GERRY LEFFERS
PRIMARY EXAMINER

Notice to Comply	Application No.	Applicant(s)	
	09/868879	Schofield et al.	
	Examiner	Art Unit	
	M. Marvich	1636	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Figures 1-8 contain sequences without SEQ ID NO:s.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY